

## **REMARKS**

### **STATUS OF THE CLAIMS**

Claims 112-162 were pending in this application. Claims 117-119, 133-135, 149-151, 160, and 162 have been amended. Following entry of the amendments claims 112-162 will be pending and at issue.

### **SUPPORT FOR AMENDMENTS TO THE CLAIMS**

Claims 117, 133, and 149 have been amended as shown above. Support can be found throughout the specification as filed, e.g., at least at claim 115.

Claims 118, 134, and 150 have been amended to delete “simple.”

Claims 119, 135, and 151 have been amended to change their dependency in view of the above amendments to claims 117, 133, and 149, respectively.

Claims 160 and 162 have been amended to include “to a human and/or animal body in need thereof” or “in need thereof” to more clearly define applicant’s invention, respectively. Support for the term “to a human and/or animal body in need thereof” can be found throughout the specification as filed, e.g., at least at page 2, paragraph 24 of the published application and Examples 1-3, as described in more detail below.

The amendments to the claims thus add no new matter and entry is respectfully requested. The amendments to the claims were made merely to further prosecution and should not be construed as abandonment or agreement with the examiner’s position in the Office Action.

### **REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH**

**Claims 112-162** were rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The examiner stated:

Claim 112 recites the terms, 'an agent'. The specification (page 5,15-18) teaches that the agent can be carbohydrate or a derivative of carbohydrate but the claim recitation is seen to include substances other than carbohydrates. The metes and bounds of the said terms recited in this and all other claims in which the said terms are recited, are unclear.

Office Action at 6.

Applicant disagrees. The specification as filed teaches that an agent can comprise a carbohydrate or an active derivative thereof or an amino acid and/or a protein. *See* p. 3, lines 31-32; and p. 4, lines 1-2 of the specification as filed. In addition, the claims as filed teach that an agent can be a carbohydrate and/or active derivative thereof and/or an amino acid and/or a protein. *See* claim 10 as filed. Also, the claims as filed teach that an agent can be a simple carbohydrate and/or a derivative of the simple carbohydrate and/or a simple sugar and/or a derivative of the simple sugar and/or glucose, sucrose and/or fructose and/or a derivative of glucose, sucrose and/or fructose. *See* claims 10-14, 29-33, 50-54, 63-67, 80-84, and 99-103 as filed.

In view of the above arguments this rejection is moot.

The examiner stated:

The term "simple" in claim 117 is a relative term which renders the claim indefinite. The term "simple" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification gives examples of simple carbohydrates but the degree of simplicity is not clear from these examples either. The said term is also recited in other claims.

Office Action at 7.

Without agreeing with the examiner, but merely to further prosecution, applicant has amended the claims as shown above. In view of the above amendments and arguments this rejection is moot.

The examiner stated:

Claim 160 recites administering a composition according to claim 112 but it is not clear to who or what the said composition is administered.

Office Action at 7.

Without agreeing with the examiner, but merely to further prosecution, applicant has amended the claims as shown above. In view of the above amendments and arguments this rejection is moot. Withdrawal of this rejection is respectfully requested.

## REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

**Claims 112-118, 120-134, 136-150, and 152-162** were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Office Action rejected this claim because “the instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without *undue experimentation*.” Office Action at 4, emphasis in original. This contention is respectfully traversed for at least the following reasons.

Applicant thanks the examiner for acknowledging that a composition comprising L-carnitine and glucose, sucrose, fructose, and/or amino acids and the method of increasing carnitine retention using the composition are enabled. Office Action at 3.

The enablement requirement of § 112 is satisfied when an application describes a claimed invention in a manner that permits one of ordinary skill to practice it, without undue experimentation. MPEP § 2164.01. Thus, the mere fact that experimentation might be required is insufficient to support an enablement rejection. Further, even complex experimentation is not necessarily undue. *Id.*

Applicant submits that undue experimentation is not required to make and use the claimed invention. In this regard, it is important to be mindful that the question of enablement is one of predictability in view of what is known in the art. Consequently, the amount of guidance or direction needed to satisfy the enablement requirement is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. MPEP § 2164.03.

The specific question of whether experimentation is “undue” is determined based on the following eight Wands factors:

1. Breadth of the claims;
2. Nature of the invention;
3. State of the prior art;
4. Level of ordinary skill in the art;
5. Predictability of the art;
6. Amount of direction provided in the specification;
7. Any working examples; and
8. Quantity of experimentation needed relative to the disclosure.

See MPEP § 2164.01(a), citing *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Further, a proper analysis of whether any experimentation is undue requires an analysis of all of the pertinent Wands factors. MPEP § 2164.01(a). It is improper to conclude that a disclosure is not enabling based on an analysis of only a subset of the above factors while ignoring one or more of the others. *Id.* In this regard, applicant notes that the examiner failed to address (1) the state of the prior art and (2) the level of ordinary skill in the art anywhere in the Office Action.

The following Wands factors weigh in favor of enablement:

**Breadth of the claims and the nature of the invention**

Independent claim 112 is directed to a composition for promoting muscle carnitine accumulation in human skeletal muscle, the composition comprising L-carnitine and an agent to increase blood plasma/serum insulin concentration, and wherein the amount by weight of said agent is at least ten times the amount by weight of said L-carnitine. Independent claim 128 is directed to a composition for promoting muscle carnitine accumulation in human skeletal muscle, the composition comprising 0.25g to 3g of L-carnitine and between 2.5g and 450g of an agent to increase blood plasma/serum insulin concentration. Independent claim 144 is directed to a composition for increasing the carnitine content of human skeletal muscle, the composition comprising L-carnitine and an agent to increase blood plasma/serum insulin concentration, wherein the agent is present in an amount sufficient to increase blood plasma/serum insulin concentration above 50 mU/l.

Applicant notes that the examiner mischaracterized the nature of the invention in the Office Action, stating: “The instant invention pertains to compositions comprising a carnitine substance and an agent to increase blood/plasma insulin concentration and method of increasing carnitine retention in animal or human skeletal muscle using the said composition.” Office Action at 4, emphasis added.

**The state of the prior art and the predictability of the art**

Applicant notes that the Wand factor relating to the state of the prior art was not directly addressed in the Office Action. *See above.*

Exhibit A is a group of references that demonstrate that:

- Various agents capable of increasing blood plasma/serum insulin concentration were known in the art. These agents include: glucose, sucrose, fructose, amino acids, raw starch, cooked starch, rice, potatoes, carbohydrate, galactose, mannose, milk chocolate bar, granola bar, chocolate milk, peanut butter cups, yogurt, potato chips, corn starch, monosaccharide, disaccharide, maltose, Caloreen, polysaccharide, starch, wheat protein hydrolysate, and protein.
- Methods for measuring blood plasma/serum insulin concentration were known in the art.

For example, Crapo et al. shows that insulin concentration increases following oral administration of simple and complex carbohydrates. *See Crapo et al. at least at Abstract, Figures 1, 2, 4, 5, and Table 2.* Shively et al. shows that insulin concentration increases following oral administration of a milk chocolate bar, a granola bar, chocolate milk, peanut butter cups, yogurt, or potato chips. *See Shively et al. at least at Abstract and Figures 1, 2, and 4.* Wahlqvist et al. shows that insulin concentration increases following administration of monosaccharides, disaccharides (maltose), an intermediate polysaccharide mixture with a mean chain length of five glucose units (Caloreen), or polysaccharides (starch). *See Wahlqvist et al. at least at Abstract, Figure 3, and Table 2.* Spiller et al. shows that insulin concentration increases following oral administration of a meal with 15.8, 25.1, 33.6, or 49.9 grams of protein along with approximately 58 grams of carbohydrate. *See Spiller et al. at least at Abstract and Figures 4-5.* van Loon et al. shows that insulin concentration increases following oral administration of amino acids and/or protein with carbohydrate. *See van Loon et al. at least at Abstract and Figures 4-6.* Westphal et al. shows that insulin concentration increases following oral administration of protein or protein plus glucose. *See Westphal et al. at least at Abstract and Figure 2.*

Thus, various agents capable of increasing blood plasma/serum insulin concentration were known in the art and methods for measuring blood plasma/serum insulin concentration before and after agent administration were known in the art.

**The level of ordinary skill in the art**

It is submitted that the level of ordinary skill in the relevant art, the scope of which is not addressed in the Office Action, is relatively high. *See above.*

**The amount of direction provided in the specification**

The examiner stated:

The instant specification (page 5, 15-18) teaches that the agent can be carbohydrate or a derivative of carbohydrate but the claim recitation is seen to include substances other than carbohydrates. Even the term carbohydrate is broad and is seen to include any carbohydrate. Proteins and amino acids are not seen in the definition. The amounts recited for the agents are also very high.

Office Action at 5.

Applicant disagrees. For example, the specification as filed teaches that an agent can comprise a carbohydrate or an active derivative thereof or an amino acid and/or a protein. *See p. 3, lines 31-32; and p. 4, lines 1-2 of the specification as filed.* In addition, the claims as filed teach that an agent can be a carbohydrate and/or active derivative thereof and/or an amino acid and/or a protein. *See claim 10 as filed.* Also, the claims as filed teach that an agent can be a simple carbohydrate and/or a derivative of the simple carbohydrate and/or a simple sugar and/or a derivative of the simple sugar and/or glucose, sucrose and/or fructose and/or a derivative of glucose, sucrose and/or fructose. *See claims 10-14, 29-33, 50-54, 63-67, 80-84, and 99-103 as filed.*

Thus the specification provides direction to one of skill as to what an agent is. The examples section of the specification as filed provides further direction to one of skill in the art, demonstrating that various agents can be administered to increase insulin levels, methods of measuring insulin levels before and after agent administration, and that direct administration of insulin with L-carnitine increases L-carnitine transport into skeletal muscle. *See below.*

### Working examples

The specification as filed provides at least three working examples. *See* Examples 1-3.

In the first example, applicant describes an experiment where subjects consumed 3.01 g (3x 1.5 g L-carnitine L-tartare effervescent tablets) L-carnitine (Lonza Group, Basel, Switzerland) dissolved in 200 ml of water. After 1 hour and then 3 more times every 1.5 hours (h), subjects consumed a 500 ml drink over a 5 min period in a randomised order containing either sugar free orange drink (Control) or 94 g of simple sugars (CHO) (Original Lucozade, GlaxoSmithKline, Brentford, UK). The method used for the determination of carnitine was based on the carnitine acetyltransferase (CAT) catalysed reaction. Insulin concentration was measured with a radioimmunoassay kit (Coat-a-Count Insulin, DPC, Ca, USA).

The results of the first example show that L-carnitine supplementation together with CHO results in a smaller loss of urinary carnitine than that seen with Control. Total (TC), free (FC) and acyl (AC) carnitine were all excreted less with CHO, than in Control. From the results it can be seen that insulin, released as a result of ingesting carbohydrate (CHO), stimulates L-carnitine retention.

In the second example, applicant describes an experiment where on each experimental visit by the subjects a 360 min euglycemic insulin (human Actrapid) clamp was performed, whilst maintaining a blood glucose concentration of  $4.4 \pm 0.01$  mmol/l via infusion of a 20% glucose solution. The insulin clamp began at  $t=0$  (FIG. 5) and varied between visits being either 5, 30, 55, or  $105 \text{ mU} \cdot \text{M}^{-2} \cdot \text{min}^{-1}$  in order to obtain a fasting, fed, physiologically high, or close to supraphysiological serum insulin concentration, respectively. Following a 60 min equilibration period, an intravenous infusion of 60 mM L-carnitine (Lonza Group, Basel, Switzerland) was begun in conjunction with the insulin clamp, which lasted for the remainder of the protocol (FIG. 5). Specifically, a bolus dose of  $15 \text{ mg} \cdot \text{kg}^{-1}$  L-L-carnitine was administered intravenously over a 10 min period in order to achieve a plasma concentration of  $\sim 500 \text{ } \mu\text{mol/l}$ . This was followed by a constant infusion at  $10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  for the next 290 min to maintain a supraphysiological steady steady state plasma carnitine concentration. At  $t=360$  both insulin and L-carnitine infusions were

stopped and subjects were free to leave the laboratory once their blood glucose levels had stabilised.

The results of the second example show that high serum insulin concentration increased sodium dependent L-carnitine transport into skeletal muscle via activation of the Na<sup>+</sup>--K<sup>+</sup>ATPase pump, resulting in a fall in plasma total carnitine.

In the third example, applicant describes an experiment where subjects reported to the laboratory in the morning after an overnight fast and underwent exactly the same experimental procedures as described in the previous example's study protocol. However, in this example two, as opposed to four, euglycaemic insulin clamps (5 and 105 mU.m<sup>-2</sup>.min<sup>-1</sup>) were performed in a randomised order, and each was separated by 2 weeks. Each clamp was maintained for 6 hours and a muscle biopsy sample was obtained from the quadriceps muscle group in the basal state (prior) to infusion of carnitine and glucose and insulin) and after 6 hrs of infusion. Analytical and statistical procedures were as described in the above noted examples, with the exception of muscle acyl, acetyl and free carnitine concentrations which were analysed according to the method of Cederblad et al. Statistical differences in muscle carnitine status was determined using Student's Paired T-test.

The results of the third example show that: (i) Carnitine per se does not readily enter the muscle compartment (even when plasma carnitine concentration is dramatically elevated). This observation is in keeping with the notion that carnitine supplementation per se does not elevate the muscle carnitine pool; and (ii) Insulin promotes muscle carnitine accumulation in the presence of elevated plasma carnitine concentrations.

Thus the working examples provide at least the following:

- Various examples of agents (e.g., glucose and CHO) that can be administered to increase insulin levels and increase L-carnitine transport into skeletal muscle.
- Methods of measuring insulin levels before and after agent administration, e.g., via a radioimmunoassay kit from Coat-a-Count Insulin, DPC, Ca, USA.
- Direct administration of insulin with L-carnitine demonstrating that increasing insulin concentration increases L-carnitine transport into skeletal muscle.

**Quantity of experimentation needed relative to the disclosure**

The examiner stated:

Prior art used in the rejections below, teaches the use of L-carnitine, its acyl derivative, amino acids and ribose in addition to glucose, fructose and sucrose. The art is silent regarding the use of any other sugar/carbohydrate and protein.

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As a result, it necessitates one of skill to perform an exhaustive search for the embodiments of using any carbohydrate or protein as recited in the instant claims suitable to practice the claimed invention.

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Indeed, in view of the information set forth, the instant disclosure is not seen to be sufficient to enable the compositions and methods of use as broadly encompassed by the recitation in the instant claims. One of skill in the art would have to carry out undue experimentation to practice the instant invention.

Office Action at 5-6, emphasis omitted.

Applicant disagrees. As is clear from the above discussion, many agents were known in the art that increase insulin concentration upon administration to a subject and methods were known for determining how a particular agent impacted insulin concentration following administration of the agent to the subject. Furthermore, the specification as filed provides direction as to what an agent is as well as multiple working examples showing that directly increased insulin concentration increases L-carnitine transport into skeletal muscle.

The enablement requirement of § 112 is satisfied when an application describes a claimed invention in a manner that permits one of ordinary skill to practice it, without undue experimentation. MPEP § 2164.01. Thus, the mere fact that some experimentation might be required is insufficient to support an enablement rejection and even complex experimentation is not necessarily undue. *Id.* In this regard, it is important to be mindful that the question of enablement is one of predictability in view of what is known in the art. Consequently, the amount of guidance or direction needed to satisfy the enablement requirement is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. MPEP § 2164.03. In this case, the specification as filed describes to one of skill in the art what an agent is (e.g., carbohydrates, proteins, amino acids, etc.) and one of skill in the art would have known of

numerous agents capable of increasing insulin concentration. *See* Exhibit A and the specification as filed. Further, one of skill could easily test whether a particular agent increases insulin concentration using known methods in the art as well as those described in detail in the specification as filed. *Id.* With these resources in hand, this level of experimentation cannot be considered undue. Thus, applicant respectfully submits that undue experimentation is not required to make and use the claimed invention.

In view of the foregoing, applicant submits that ordinarily skilled artisans would be able to make and use the claimed invention, despite any experimentation that might be required. Applicant further submits that this conclusion is buttressed by the amount of knowledge in the state of the art as well as the predictability of the art, as well as the majority of Wands factors that weigh in favor of enablement. Therefore, the application as filed adequately enables the claimed invention.

Applicant thus respectfully requests favorable reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

## **REJECTIONS UNDER 35 U.S.C. § 102**

**Claims 112-162** were rejected under 35 U.S.C. § 102 as allegedly being unpatentable over Pola (WO 01/95915, of record). Applicant traverses this ground of rejection by argument.

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention.

The examiner stated:

Pola teaches a composition comprising L-carnitine (250mg), ribose (1g), dextrose (misspelled as destrose; another name for glucose; 0.5g), fructose (0.5g). In this composition ribose, dextrose and fructose are the agents for increasing the blood/serum insulin concentration (as recited in instant claims 116-119; 132-135; 148-151). In the composition of Pola the total amount of the carbohydrates ribose, dextrose and fructose (the agent) is 2g. L-carnitine is 250mg, which 0.25g. Hence, the ratio of the agent to the L-carnitine by weight is 10:1 (limitations of instant claims).

Office Action at 7-8, emphasis added.

Applicant notes that a ratio of 2 grams of sugars (ribose, dextrose, and fructose) to 0.25 grams of L-carnitine is not a literal 10:1 ratio. Thus, the cited art does not teach each and every element of the claimed invention and cannot anticipate the claimed invention under 35 U.S.C. § 102.

Applicant notes that the examiner did not address the claim limitations of independent claims 128 and 144 or their respective dependent claims. Applicant requests clarification as to whether these claims are allegedly anticipated by Pola or if they are in condition for allowance.

Accordingly, the reference does not teach each and every element of the claimed invention and cannot anticipate the claimed invention. Withdrawal of this rejection is requested.

## CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (415) 875-2352.

Respectfully submitted,

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